MEMORANDUM

Date: December 5, 2008

From: Alan Trounson, Ph.D., CIRM President

To: Independent Citizens Oversight Committee

Subject: Extraordinary Petition for Application RT1-01067

Enclosed is a letter from Dr. Babak Esmaeli-Azad, of DNAmicroarray, Inc, an applicant for funding under RFA 08-02, CIRM Tools and Technologies Awards. This letter was received at CIRM at least five working days prior to the December ICOC meeting, and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

As required by that policy, I have reviewed the petition (referencing reviewer comments and the submitted application as necessary) in consultation with Dr. Csete and the scientific staff, and concluded that the petition does not present compelling evidence that should alter the recommendation or score of the Grants Working Group (GWG). First, the applicant's assumption that our processes include a "dual level of review" is mistaken. CIRM Science Officers did not evaluate the merit of the applications in any way, but collated information for the review summaries from the written and oral discussions by the GWG. Second, the applicant has numerous complaints about the scientific reviews that fall into the realm of scientific disagreement. CIRM stands behind the reviewer's specific comments as being valid scientific critiques and the overall conclusion that the application was not competitive in this highly competitive round of applications. We disagree with the suggestion that the applications were reviewed "using the same rubric as an academic enterprise". In fact, GWG reviewers were specifically instructed to consider the industry achievements (successful project leadership and management) of industry applicants, and not to consider peer-reviewed publications as a necessary part of the track record of industry applicants. CIRM staff will be prepared to provide further analysis, should that be requested by any member of the committee.

Redactions, if any, have been made pursuant to the policy, in consultation with the author(s) of the letter. An unredacted version will be available for review in closed session.

The enclosed letter represents the views of its author(s). CIRM assumes no responsibility for its accuracy.

In addition, a copy of the CIRM Review Summary for this application is provided for reference.

TO: The Chairman of the ICOC, President of CIRM, and Chief Scientific Office of CIRM
FROM: DNAmicroarray, Inc.SUBJECT: Extraordinary Petition DATE: December 2, 2008

In accordance with the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding, we hereby submit the following for your kindly consideration. Based on our analysis of the Review Report - CIRM Tools and Technologies Awards Application (RT1-01067-1: Biomaterial Microenvironment Modeled Bioreactor) received by DNAmicroarry, Inc., via e-mail on November 25, 2008, we believe the Grants Review Working Group's (GRWG) review was flawed and that the process associated with the review is arbitrary and capricious.

Concerning the process, formal appeal is limited to instances of demonstrable conflict of interest, yet we are not given a roster listing the actual persons that reviewed the proposal, as certainly all of the members listed for the Scientific and Medical Research Funding Working Group do not read and evaluate each proposal. Further, as we understand from a communication with Dr. Gilberto Sambrano, Scientific Review Officer, CIRM, it is impossible to determine the reviewers for any particular application because the review report is generated second-hand through interpretation by CIRM staff of one or more reviewer's comments, and is not a report generated by the reviewers themselves. This dual level of review results in further ambiguity and opacity of the process, in effect making appeal impracticable. Accordingly, in view of this impracticality and the flaws in the review (as we outline below), we submit that extraordinary circumstances exist such that the instant petition is warranted.

As recited in CIRM RFA-08-02, the standard of review is primarily focused on three areas 1) impact of the research to overcome current road blocks and advance the stem cell field, 2) design and feasibility of the research plan, and 3) qualifications of the Principal Investigator and the research team. However, the comments recited in the review demonstrate that conclusions provided by the GRWG are not internally consistent. For example, while the reviewers readily admit that the methods disclosed in the proposal would have "significant utility" and "would be potentially of significant value, especially for clinical applications," in the very next paragraph, they conclude that "[t]he probability that the results of this work will move the field significantly forward was thought to be low."[1] Further, while conclusory statements were offered to support positions related to specific goals as outlined (e.g., "reviewers felt that the proposed research plan does not provide a clear path to these goals"), many of the conclusions offered (a) did not seem to be based on the proposal as written (e.g., clarity about "what niche they wish to produce") or (b) were directed to methods/goals expressly excluded by the PI (e.g., "filtering and separation of specific progenitors from all other cell types").

To amplify the latter point first (i.e., point (b)), the review recites that the plan for a comprehensive approach to the problem of scale-up was incomplete, emphasizing that the second aim, by not isolating differentiated cells free of potentially tumorigenic undifferentiated stem cells, does not represent a step that completely overcomes a major roadblock in stem cell biology. This conclusion is irrelevant because, as expressly recited in the Rationale and Significance Section, p. 2, first paragraph, ll. 22-26, including the associated Figure, separation of specific cell types (e.g., "tumorigenic undifferentiated stem cells") is not the subject of this proposal and is currently under investigation in-house. Regarding the "comprehensive approach" remark, the proposal clearly emphasizes that generation of specific lineages and/or cell types (i.e., the subject of the instant proposal) is a pre-requisite, and that separation/isolation of specific cells in conjunction with said generation represents the

[1] In contrast to this position, since this proposal was written we have communicated its contents to several CIRM grantees recognized as national and international leaders in the field of hESC, these individuals were desirous of the bioreactor system as disclosed and indicated that our proposed studies would effectively achieve the milestones as recited.

comprehensive approach. Notwithstanding, given the criticality of the generation step, both lineage generation and separation as envisaged could not have been effectively accomplished within the time constraints and funding limitations of the Tools and Technologies RFA. As such, the conclusions based on this section of the review are inappropriate and should not have been used in the decision matrix (i.e., impact of the research to overcome current road blocks and advance the stem cell field).

To amplify the former point (i.e., point (a)), the reviewers recite that "cell types utilized in the first specific aim are not ideally suited to the research," stating that the cells as disclosed are "inappropriate for clinical translation or for the ultimate production of clinically useful human cells," including that "reviewer's found that applicants are rather unclear about what specific niche they wish to produce." These assertions demonstrate a profound misunderstanding of how R&D is to be conducted in a corporate/industrial setting. This proposal is focused on the development of a novel scalable 3-D bioreactor technology for the production of stem and/or primitive progenitor cells. Specific Aim 1 describes the process flow which results in the transition from "breadboard" prototype to a laboratory prototype, ultimately establishing an ability to co-culture a more sophisticated stimulant of stem and/or primitive progenitor cells (i.e., co-culture of mouse stromal cells and cord blood embryonic-like stem cells (CBEs)). The goal of Step 1 is to design and develop "breadboard" prototype bioreactor hardware, test, refine, and optimize its performance in simulated scenarios using low cost, easy to use, readily available simulants (i.e., HeLa cells, see p. 3, Section B). Step 2 is to further demonstrate the feasibility of the prototype using stromal cells alone, as these cells serve as a model/simulant for feeder layer cells (see, e.g., p. 3, Section B). In Step 3, cell loading and homing into this feeder layer simulant is developed and optimized using CBEs. By the end of step three, the laboratory prototype of said bioreactor is developed to a point where it may be used for studies outlined in Aim 2.

We would like to emphasize that the use of simulants is a standard in the industry because it provides a means for comprehensive testing and analysis of any prototype in different stages of development in the most cost effective and efficient manner. These types of studies are crucial to industrial product development as robust functionality is a requisite minimum for any prototype. We appreciate that academic goals of generation of publications would not require such R&D, but we vehemently protest being reviewed using the same rubric as an academic enterprise. Further, the simulants were chosen based on their previously established properties, including, but not limited to, simulation of engraftment in vivo (e.g., to establish homing properties for loading the device; see Research Design and Methods, p. 6, Aim 1-3, Section B) as well as the fact that protocols for separation and identification of this simulant (e.g., CBEs) have been well established, thus permitting facile interpretation of experimental results.

Applicants would remind the reviewers that CBEs are an excellent choice for a simulant in the instant proposal since they have been clearly demonstrated to be pluripotent, typically expressing embryonic stem cell markers, including Oct4 and Sox2 (see, e.g., McGuckin et al., Nat Protoc (2008) 3(6):1046-55). It has also been extensively demonstrated that CBEs give rise to multiple progenitor lineages (Id.), transplantations of which are routinely used for treatment of hematopoietic diseases, including, but not limited to, AIDS (see, e.g., Behringer et al., Stem Cells Dev Nov 19 [Epub ahead of print] PMID:19018697). Regarding the remarks concerning the specific niche, clearly the proposal is designed to establish a microenvironment niche in vitro for propagation of hESCs as well as directed differentiation into progenitors of the hematopoietic lineage (see, e.g., p. 4, Specific Aims, Milestones and Timelines, Aims 2-1 to 2-3; pp. 7-9, Research Design and Methods, Aims 2-1 to 2-3). Regarding the remark that "the reviewers criticized their approach to simply adapt previously published work to the context of a bioreactor, rather than working[sic] refine and improve the culture environment," as clearly stated at p. 4, Specific Aims 2-1 and 2.2 and Research Design and Methods, p. 7, Specific Aim 2, a novel

enabling high throughput 3-D screening technology (Cell matrix Arrays™, see also www.dnamicroarray.com/cell_matrix_arrays.htm) will be used as a tool to translate previously published findings to the 3-D culture microenvironments and ultimately to the bioreactor. This is a fundamental reason why the proposed R&D has generated a high level of enthusiasm for this platform as clearly indicated by leaders in this field (see FN1), and in the LOS from [redacted] Therefore, as with point (b), the conclusions recited in this section of the review are inappropriate and should not have been used in the decision matrix (i.e., design and feasibility of the research plan).

In reference to the summary paragraph related to the design and logic of the proposal, applicants would point to paragraphs (4) and (5) above, and again submit that the conclusions based on this section of the review are inappropriate and should not have been used in the decision matrix.

Regarding the remarks related to PI and team qualifications, at no time in this proposal does the PI claim to have track record of leadership in the stem cells field or extensive experience with novel bioreactor systems. The PI, on the other hand, has more than eighteen years of professional product development experience, including drug discovery and development, diagnostic and research tools development and commercialization, both in large (Fortune 500) and small biotech and pharmaceutical companies. In addition, during the last 11 years, the PI's accomplishments in this area have been the main driver for profitable organic growth of applicant institution. Again, as intimated above, using the same rubric for review as one would a PI of an applicant academic entity is problematic, because reliance on publications and academic accomplishments woefully underestimate the skill of the instant PI, whose skills are critical for industrial development and production of commercial products.

To provide extensive experience both in the area of stem cell space and novel bioreactor systems, we secured partnerships with internationally recognized industrial and academic consultants for this project. The criticism that the plan relies heavily on scattered consultants (California, Utah, Texas) seems to discount today's realities of how top quality research is typically being carried out. The reality is that collaborations are always based on technologies and ideas, and never on the basis of proximity alone, this is readily apparent given CIRM's current program of outreach to promote international collaborations. Further, a quick review of the roster of the GRWG clearly demonstrates that none of the members' scientific work is limited to local collaborations. Therefore, the statement that such collaborations "may be problematic" is a non-sequitur.

Regarding the remark related to the "consultant with the most expertise," it is unclear as to how 1) this assessment was made given the qualifications of the other consultants recited in the proposal and 2) the letter was adjudged to be incomplete. Notwithstanding the first point, we can only deduce that the reviewers have concluded that the electronic signature was insufficient. We submit that all of the consultants were willing participants, and that the consultant in question would be willing to provide any alternative form of attestation that you might require.

Regarding the concerns about the proposed budget, again, we would like to emphasize that industrial standards are different from academic standards, especially in view of product development where the relative reliability and robustness of prototypes is of a higher order than that required to publish results in a scientific journal. Further, these types of studies are crucial to industrial product development as robust functionality is a requisite minimum for any prototype. As such, given the rigors of the testing regime as recited in the proposal, the amounts requested are in-line with the goals of the project.

In view of the reasons above, we submit that the Grants Review Working Group's (GRWG) review was flawed and that the process associated with the review is arbitrary and capricious, and respectfully request that the instant proposal (RT1-01067-1: Biomaterial and Microenvironment Modeled Bioreactor) be recommended for funding.